Special Article

Summary of the Dutch Multidisciplinary Practice Guideline on Asthma and Pregnancy

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KEY RECOMMENDATIONS

- The possibility of preconception counseling should be offered at least once to every woman of reproductive age with asthma.
- Continue current asthma medication during pregnancy when asthma is well controlled.
- Identify and treat potential risk factors leading to uncontrolled asthma and/or adverse pregnancy outcomes prior to pregnancy or as early as possible in pregnancy.
- Asthma patients with identified risk factors should receive intensified monitoring, in which the multidisciplinary developed flowchart may be helpful.
- A multidisciplinary collaboration is required for the management of severe asthma in pregnant women.

ABSTRACT: Asthma is the most common chronic respiratory disease in women of childbearing age and during pregnancy. This paper presents a summary of the Dutch multidisciplinary guideline on asthma and pregnancy. The aim of this guideline is to provide structured, where possible, evidence-based recommendations to optimize the management of asthma during pregnancy. The main topics covered in this guideline are preconception counseling, the safety of asthma medications during pregnancy and breastfeeding and risk assessment and monitoring of asthma during pregnancy. Because many caregivers are involved and a uniform approach is desirable, this guideline has been developed in collaboration with all relevant health care providers and patient representatives. **© 2024 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2024;12:1751-62)**

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SHOUT
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Abbreviations used
ACQ- Asthma Control Questionnaire
AGREE- Appraisal of Guidelines for Research and Evaluation
BTS- British Thoracic Society
ERS/TANZ- European Respiratory Society/Thoracic Society of Australia and New Zealand
FeNO- Fractional exhaled nitric oxide
GINA- Global Initiative for Asthma
GRADE- Grading of Recommendations Assessment, Development, and Evaluation
ICS- Inhaled corticosteroids
IL- Interleukin
LABA- Long-acting β-agonist
LAMA- Long-acting muscarinic antagonist
LTRA- Leukotriene receptor antagonist
NVALT- Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose
OCS- Oral corticosteroids
OTIS- Organization of Teratology Information Specialists
RCT- Randomized controlled trial
SABA- Short-acting β-agonist
SAMA- Short-acting muscarinic antagonist

INTRODUCTION

Asthma is the most common chronic lung disease during pregnancy. The course of asthma during pregnancy can be unpredictable. More than a third of patients experience worsening of asthma symptoms during pregnancy.[1,2] Asthma exacerbations during pregnancy have been found in 20% to 45% of patients, with severe exacerbations requiring treatment with oral corticosteroids (OCS) in about 10%.[3,4] Uncontrolled asthma and exacerbations during pregnancy are associated with an increased risk of adverse pregnancy outcomes (eg, pre-eclampsia),[5-7] neonatal outcomes (eg, low birth weight and preterm birth),[8-10] and child outcomes (eg, risk of asthma).[11-13] Well-controlled asthma contributes to better outcomes for both mother and child.[6,14]

With good (preconception) counselling, unambiguous advice on medication safety, and adequate monitoring, outcomes for pregnant women with asthma are generally good.[6,15] This guideline describes the management of women with asthma at all stages of pregnancy. A significant part of this guideline focuses on the use of asthma medications during pregnancy and breastfeeding. This includes recommendations on relatively new medications, such as biologics, that are increasingly being used to treat severe asthma. Attention is also given to the monitoring of asthma during pregnancy. Lastly, the guideline has identified gaps in our current knowledge of asthma and pregnancy and calls for more scientific evidence to support existing care for this group of patients.

The aim of this multidisciplinary guideline is to provide structured and, where possible, evidence-based standard of care for pregnant patients with asthma. The guideline has been developed for all health care providers involved in the care of pregnant women with asthma, including not only pulmonologists, allergists, obstetricians, respiratory nurses, and midwives but also pharmacists and general practitioners. Furthermore, patient representatives were actively involved in the development of this guideline. The multidisciplinary nature of this guideline aims to ensure continuity of care and consistency of advice from different health care providers involved. This article summarizes the key recommendations of the "Dutch multidisciplinary guideline on asthma and pregnancy" and briefly addresses the evidence and rationale for most important recommendations.

METHODS

The development of this guideline was initiated by the Dutch Association of Pulmonologists (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose [NVALT]). A multidisciplinary working group included all relevant specialists (pulmonology, gynecology, obstetrics, pharmacy, and primary care) and representatives of patients. The process was supported by the national Knowledge Institute of the Dutch Association of Medical Specialists, Utrecht, The Netherlands. Internationally, this is the first guideline on asthma and pregnancy, based on the "Appraisal of Guidelines for Research and Evaluation" (AGREE II) and the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) methodology, from a multidisciplinary working group including patients' perspectives.[16]

The scope of the guideline was determined by problem identification by all stakeholders. Prioritized problems were converted into clinical questions and defined by Patients/Population, Intervention, Control, Outcome research questions. Literature searches were conducted by literature specialists. Strength of evidence was determined by the GRADE method. When GRADE was not possible, because studies found by the literature search did not meet the inclusion criteria, studies were described in the rationale if relevant for the direction of the recommendations. Search terms and strategies are described in detail in the Online Repository and full guideline (available in this article's Online Repository at www.jaci-inpractice.org).[17]

The assessment of the literature by using GRADE differs from previous assessments by the British Thoracic Society (BTS) and Global Initiative for Asthma (GINA).[18,19] This difference is mostly due to the method used to assess the evidence from the literature. The GRADE evaluates the quality of the evidence based on outcomes rather than on the design of a study. In addition, levels of inconsistency, imprecision, indirectness, and potential publication bias are evaluated for each outcome and may affect grading of the literature.

RECOMMENDATIONS

Preconception counseling

Recommendations (no GRADE).

- Health care providers need to discuss pregnancy planning with every woman of reproductive age with asthma at least once and offer the possibility of preconception counselling.
- A clear overview of the recommendations regarding preconception counseling is provided in Table I.

Rationale. The preconceptual period is a window of opportunity. It is the only time when risk factors can be identified and possibly reduced before they have potential adverse effects on outcomes for both mother and child.[20,21] It promotes the health of both future parents and future children and aims to give future parents as much freedom as possible to make their own reproductive choices. It is, therefore, important to discuss contraception and childbearing regularly with women with asthma during

TABLE I. Preconception counseling

General recommendations	Inform women with asthma and their partners about the following:
- When prescribing new asthma medications to women of reproductive age, proactively ask about pregnancy planning and advise them to always consult a health care provider in a timely manner. - Perform intercollegial consultation for women with severe asthma, complex comorbidities, or multiple risk factors with a gynecologist or preferably in an MDT meeting. - Consider the use of supporting materials to promote self-management such as an PAAP.	- Inform women that well-controlled asthma does not adversely affect the course and outcomes of pregnancy and delivery. - Educate women about the importance of preventing asthma exacerbations and reacting proactively when asthma exacerbations do occur. - Explain the potential adverse effects of poor asthma control on pregnancy outcomes, such as preterm birth and low birth weight. - Discuss the expected natural course of asthma during pregnancy with a peak in symptoms during the second trimester and reassure about possible complications during delivery. - Advise women to achieve well-controlled asthma before stopping contraception, whenever possible.
Emphasize the importance of	Reassure regarding the use of asthma medications
- Asthma monitoring and, if necessary, optimizing asthma medication prior to pregnancy. - Living a healthy lifestyle to prevent the risk of pregnancy complications and maintain the health of mother and child. - Advise and provide support for smoking cessation. - The generally accepted beneficial effect of breastfeeding on reducing the risk of developing asthma in the child.	- Discuss any concerns the patient and/or partner may have about adverse effects of asthma medication. - Discuss that medications are not usually stopped, but may be adjusted preconceptually. - Discuss the risks of discontinuing asthma medications or nonadherence during pregnancy and postpartum. - Discuss that most current asthma medications can be continued during breastfeeding.

MDT, Multidisciplinary team; *PAAP,* Patients/Population, Intervention, Control, Outcome.

their fertile years. Furthermore, it is important to realize that asthma is associated with a longer time to pregnancy, especially as a women ages.[22,23]

SAFETY OF ASTHMA MEDICATIONS

General recommendations for asthma medication use during pregnancy

Recommendations (GRADE D).

- Continue current asthma medication during pregnancy when asthma is well controlled. This is safer and leads to fewer complications than accepting uncontrolled asthma without pharmacological therapy.
- As a pharmacist, assess the need for pregnancy-related medication advice for every female asthma patient of reproductive age.

Rationale. Well-controlled asthma with pharmacological therapy during pregnancy is safer and leads to fewer complications than accepting ongoing asthma symptoms and exacerbations. The working group's opinion is shared by many other researchers.[24,25] However, this view is not universal. A feeling of uncertainty about safety of asthma medication during pregnancy is often experienced by pregnant women, which can lead to non- or undertreatment.[26] Therefore, education, risk assessment, and shared decision making must be essential parts of asthma care during or even before pregnancy. For short-acting β-agonists (SABAs), long-acting β-agonists (LABAs), short- and long-acting muscarinic antagonists (SAMAs and LAMAs), inhaled corticosteroids (ICS), OCS, leukotriene receptor antagonists (LTRAs), and most biologics, a safety assessment of asthma medications during pregnancy based on the literature is provided later. Of note, no assessments were performed for specific combinations of inhaled medications with the exception of combined ICS/formoterol "as needed," because in general, the safety risk of combinations was assumed to be cumulative to their components. Tezepelumab was not assessed because it was not yet available in The Netherlands when the grading process started.

When specific questions arise about the safety of asthma medications during pregnancy, breastfeeding, or for women planning a pregnancy, it is important to ensure that patients receive unambiguous advice from the different health care providers involved. A shared view among all caregivers to not to change medications unless necessary reinforces the message. For additional information, other available resources with up-to-date information can be consulted (eg, available sources in 2023 were LactMed Drugs and Lactation Database, Netherlands pharmacovigilance centre Lareb [https://www.lareb.nl] and the Organization of Teratology Information Specialists (OTIS) (https://mothertobaby.org/).

Short-acting β-agonists

Recommendations (GRADE D).

- Continue current SABA use, as reliever therapy, for the treatment of pregnant women with asthma when their asthma is well controlled.
- If SABA overuse is observed, (re)consider the use of maintenance therapy.

Rationale. An increased risk of major congenital malformations for pregnant patients using SABAs was suggested by a meta-analysis of 3 separate congenital anomaly registries (odds ratio [OR] 1.21; 95% confidence interval [95%CI] 1.07−1.37).[27] However, registry analyses lack accuracy in differentiation between disease-specific effects and drug-induced effects and confounding may lead to bias. Two large cohort studies[28,29] and 2 case-control studies[30,31] did not show an increased risk of major congenital malformations (pooled OR 1.10, 95% CI 0.90−1.35 and OR 1.37, 95% CI 0.66−2.84, respectively). No other increased risks for pregnancy-related outcomes were found[32-38] (Table II). Based upon GRADE D evidence, the working

TABLE II. Risk of adverse outcomes from inhaled medicines in pregnant women with asthma

	SABA		LABA		SAMA LAMA	ICS	
Adverse outcomes	**Risk**	**Explanation**	**Risk**	**Explanation**	**Risk**	**Risk**	**Explanation**
Major congenital malformations	Unlikely	4 studies no risk (Eltonsy, 2011,[28] Kallen, 2007,[29] Lin, 2009,[30] Tata,[31] 2008), 1 registry meta-analysis increased risk (OR 1.21; 95% CI 1.07−1.37) (Garne, 2016[32])	No	3 studies no risk (Eltonsy, 2011,[28] Kallen, 2007,[29] Tata, 2008[31]), 1 registry meta-analysis no risk (Garne, 2016[32])	No data	Unlikely	2 meta analyses no risk (Rahimi, 2006,[33] Murphy, 2013[34]), 2 studies no risk (Blais, 2007,[35] Tata, 2008[31]), 1 registry meta-analysis increased risk (OR 1.20; 95% CI 1.04−1.38) (Garne 2016[32])
Malformation cleft lip or palate	No	1 study, n = 9 of 23,751 (RR 1.4; 95% CI 0.5−4.1) (Vasilakis-Scaramozza, 2013[36])	No	1 study, n = 1 of 23,751 (RR 2.4; 95% CI 0.3−21.8) (Vasilakis-Scaramozza, 2013[36])	No data	No	1 study, n = 5 of 23,751 (RR 1.3; 95% CI 0.1−14.0) (Vasilakis-Scaramozza, 2013[36])
Musculoskeletal congenital anomalies	No	1 study, n = 18 of 23,751 (RR 1.0; 95% CI 0.5−2.1) (Vasilakis-Scaramozza, 2013[36])	No	1 study, n = 2 of 23,751 (RR 1.9; 95% CI 0.4 to −9.1) (Vasilakis-Scaramozza, 2013[36])	No data	No	1 study, n = 13 of 23,751 (RR 1.2; 95% CI 0.5−2.5) (Vasilakis-Scaramozza, 2013[36])
Cardiovascular anomalies	No	1 study, n = 36 of 23,751 (RR 1.3; 95% CI 0.8−2.1) (Vasilakis-Scaramozza, 2013[36])	No	1 study, n = 2 of 23,751 (RR 1.9; 95% CI 0.2−4.4) (Vasilakis-Scaramozza, 2013[36])	No data	No	1 study, n = 23 of 23,751 (RR 1.0; 95% CI 0.6-1.7) (Vasilakis-Scaramozza, 2013[36])
Small for gestational age	No	1 study, n = 169 of 2,201 (RR 1.0; 95% CI 0.99−1.01) (Bracken, 2003[37])	No	1 study, n = 168 of 2,201 (RR 1.10; 95% CI 0.39−3.11) (Bracken, 2003[37])	No data	No	1 study, n = 32 of 738 (OR 1.55; 95% CI 0.77−3.10) (Bakhireva, 2005[38])
Low birth weight	No data	No data	No	No data	No data	No	1 meta-analysis (OR = 0.89; 95% CI 0.69−1.16) (Rahimi, 2006[33])
Preterm birth	No	1 study, n = 152 of 2,201 (RR 1.01; 95% CI 1.00-1.02) (Bracken, 2003[37])	No	1 study, n = 153 of 2,201 (RR 0.99; 95% CI 0.97-1.02) (Bracken, 2003[37])	No data	No	1 meta-analysis (OR 1.00; 95% CI 0.77−1.25) (Rahimi, 2006[33])
Pregnancy-induced hypertension	No data	No data	No	No data	No data	No	1 meta-analysis (OR 0.97; 95% CI 0.84−1.20 (Rahimi, 2006[33])
Stillbirth	No data	No data	No	No data	No data	No	1 meta-analysis (OR 0.77; 95% CI 0.50−1.18) (Murphy, 2013[34])
Spontaneous abortion	No data	No data	No	No data	No data	No	No data

TABLE III. Risk of adverse outcomes from other pharmacological therapies in pregnant women with asthma

	OCS		LTRA		Anti-IgE		
Adverse outcomes	**Risk**	**Explanation**	**Risk**	**Explanation**	**Risk**	**Explanation**	**Other biologics**
Major congenital malformations	Unlikely	1 study, n = 262 of 35,177 (OR 1.23; 95% CI 0.89−1.69) (Tata, 2008[31]), 1 registry meta-analysis increased risk (OR 1.48; 95% CI 1.11−1.90) (Garne, 2016[32])	Unlikely	1 study, n = 19,751 of 667,280 (OR 1.4; 95% CI 0.9−2.3) (Cavero-Carbonell, 2017[40])	No	1 study, n = 120 of 1,347 (8.1% omalizumab vs 8.9% controls; NS) (Namazy, 2020[42])	No data
Malformation cleft lip or palate	No	1 study, n = 5 of 23,751 (RR 1.3; 95% CI 0.1−14.0) (Vasilakis-Scaramozza, 2013[36])	No data	No data	No data	No data	No data
Musculoskeletal congenital anomalies	No	1 study, n = 5 of 23,751 (RR 0.7; 95% CI 0.2-2.6) (Vasilakis-Scaramozza, 2013[36])	No data	No data	No data	No data	No data
Cardiovascular anomalies	No	1 study, n = 3 of 23,751 (RR 0.9; 95% CI 0.3−3.2) (Vasilakis-Scaramozza, 2013[36])	No data	No data	No data	No data	No data
Small for gestational age	No	1 meta-analysis (RR 0.81; 95% CI 0.48−1.34) (Namazy, 2013[43]), 1 study, n = 22 of 413 (OR 1.82; 95% CI 0.65−5.08) (Bakhireva, 2005[38])	No data	No data	No	1 study, n = 204 of 1,383 (9.7% omalizumab vs 15.8% controls; NS) (Namazy, 2020[42])	No data
Low birth weight	Possible	1 meta-analysis, n = 311 of 2,608 (RR 1.41; 95% CI 1.04−1.93) (Namazy, 2013[43]), 1 study decreased risk, n = 2,201 of 32,892 (OR 3.37; 95% CI 1.66 −6.86) (Bracken, 2003[37])	No	1 study no risk, n = 168/ of 2,201 (OR 0.94; 95% CI 0.65−1.36) (Bracken, 2003[37])	No	1 study, n = 144 of 1,383 (13.7% omalizumab vs 9.8% controls; NS) (Namazy, 2020[42])	No data
Preterm birth	Likely	1 meta-analysis increased risk n = 369 of 2,608 (RR 1.51; 95% CI 1.15−1.98) (Namazy, 2013[43]), 1 study no risk, n = 2,201 of 28,956 (OR 1.01; 95% CI 0.24-4.31) (Bracken, 2003[37])	No	1 study no risk, n = 151 of 2,205 (OR 1.00; 95% CI 0.87−1.14) (Bracken, 2003[37])	No	1 study, n = 164 of 1,383 (15.0% omalizumab vs 11.3% controls; NS) (Namazy, 2020[42])	No data
Pregnancy-induced hypertension	No data	No data	No data	No data	No data	No data	No data
Stillbirth	No data	No data	No data	No data	No data	No data	No data
Spontaneous abortion	No data	No data	No data	No data	No data	No data	No data

IgE, Immunoglobulin E; *NS,* not significant.

group considers SABA use safe during pregnancy for asthma patients.

Other concerns are SABA-only treatment and/or SABA overuse. In The Netherlands, SABA-only use is still widespread despite GINA recommendations.[39] For practical reasons, SABA-only is reluctantly accepted when asthma is well-controlled and used 2 or fewer times a week. In all other cases, addition of ICS is recommended. SABA overuse (using SABA more than twice a week and/or > 2 SABA canisters dispensed in a year) is an indicator of uncontrolled asthma and must prompt reevaluation by a general practitioner or pulmonologist.

Long-acting β-agonists (LABA)

Recommendations (GRADE D).

- Continue current LABA use in pregnant women with asthma when their asthma is well controlled.
- Preferably use LABA with most experience during pregnancy (formoterol or salmeterol).

Rationale. No increased risk for major congenital malformations was found (OR 1.20; 95% CI 0.80−1.80).[27-29,31] Also, no other increased risks for pregnancy-related outcomes were found (Table II). Of note, the studies did not distinguish between the different LABAs salmeterol or formoterol. Because the studies were performed before the introduction of the LABA vilanterol, a separate literature search was conducted for safety data on vilanterol during pregnancy, but no studies were found. Based upon GRADE D evidence, the working group considers traditional LABA use safe during pregnancy for asthma patients.

Short- and long-acting muscarinic antagonists

Recommendations (GRADE D).

- Continue current SAMA and/or LAMA in pregnant women with difficult-to-treat or severe asthma when their asthma is well controlled.
- Consider SAMA use as a safe and effective alternative treatment option for SABA if SABA treatment is not sufficient.
- Consider LAMA use as a safe, but in general, less effective alternative treatment option, if LABA treatment is not sufficient.

Rationale. No clinical studies were available. However, SAMA and LAMA have been used as an add-on or alternative therapy for the treatment of asthma for decades, without reported pregnancy-related safety concerns. In animal research, high doses showed toxicity to the fetus, but no teratogenic effects were observed.[24,40] In humans, plasma levels are low owing to the administrative route. Moreover, during pregnancy, distribution volume is increased. As such, the European Respiratory Society/Thoracic Society of Australia and New Zealand (ERS/TANZ) task force considers SAMA and LAMA as safe.[24] The working group takes into account that the theoretical risks do not outweigh the proven risk of uncontrolled asthma during pregnancy. Based upon GRADE D evidence, the working group considers SAMA and LAMA use safe for patients with asthma during pregnancy. Pregnant women with asthma using SAMA or LAMA may be advised to register in drug safety monitoring registers; for example, mothertobaby.org/pregnancy-study.

Inhalation corticosteroids

Recommendations (GRADE D).

- Continue current ICS use in pregnant women with asthma when their asthma is well controlled.
- In uncontrolled asthma, (re)consider ICS treatment options and preferably choose from ICS with most experience during pregnancy (budesonide, beclomethasone, and fluticasone).

Rationale. An increased risk of major congenital malformations for pregnant patients using ICS was suggested by the meta-analysis of anomaly registries (OR 1.20; 95% CI 1.04−1.38).[32] However, 2 large meta-analyses found no significant effect of ICS on major congenital malformations (OR 0.96; 95% CI 0.47−1.96[33] and relative risk [RR] 0.96; 95% CI 0.89−1.04[34]). In addition, 2 other studies not included in these meta-analyses found no increased risk.[31,35] Also, no other increased risks for pregnancy related outcomes were found (Table II). Based upon GRADE D evidence, the working group considers ICS use safe during pregnancy for asthma patients. Furthermore, the working group points out that the use of ICS is essential for asthma control.

Oral corticosteroids

Recommendations (GRADE D).

- Treat an asthma exacerbation during pregnancy with OCS according to current guidelines as in nonpregnant women.
- Consider consulting an internist, gynecologist, and/or pediatrician for pregnant women with asthma, who are treated frequently and/or daily with OCS, because of the risk of developing secondary adrenal insufficiency in both the mother and the child.
- Pregnant women with asthma using 5 mg or greater daily prednisolone equivalent during the 3 weeks prior to delivery should be treated with corticosteroid replacement therapy during labor.

Rationale. An increased risk of major congenital malformations for pregnant patients using OCS was suggested by the meta-analysis of anomaly registries (OR 1.48; 95% CI 1.11−1.90).[32] However, 1 large case-control study found no significant effect of OCS on major congenital malformations (OR 1.23; 95% CI 0.89−1.69)[31] (Table III).[32,34,36-38,41,42]

Increased risks on low birth weight and preterm birth in pregnant patients using OCS were found in a meta-analysis of 2 studies (RR 1.41; 95% CI 1.04−1.93; and RR 1.51; 95% CI 1.15−1.98, respectively).[43] In contrast, another cohort study showed a decreased risk on low birth weight (OR 3.37; 95% CI 1.66−6.86) and no increased risk for preterm birth in pregnant patients using OCS (OR 1.01; 95% CI 0.24−4.31)[37] (Table III).

Taken together, the working group concluded that, for OCS use, an increased risk for congenital malformations is unlikely. However, an increased risk for low birth weight is possible and for preterm birth likely. Despite these concerns, the working group advises treating an asthma exacerbation during pregnancy with OCS according to current guidelines as in nonpregnant women. The theoretical risks of OCS use do not outweigh the proven risk of uncontrolled asthma during pregnancy.

Leukotriene receptor antagonists

Recommendation (GRADE D).

- Be cautious about using LTRAs during pregnancy because of a weak association with congenital malformations.

Rationale. One cross-sectional observational epidemiological study investigated data obtained from Danish birth, patient, and prescription registries.[41] After adjustment for time period, maternal age, education, and parity, and compared with a rate of congenital anomalies of 3.0% (19,751 of 667,280) in the "population group," the study showed that the rate of congenital anomalies was 4.4% (16 of 364) in the "montelukast only" group (OR 1.4; 95% CI 0.9−2.3), 3.1% (12 of 384) in "montelukast and other" group (OR 1.0; 95% CI 0.6−1.8), and 3.3% (739 of 22,705) in the "other asthma medications" group (OR 1.1; 95% CI 1.0−1.2). No other increased risks for pregnancy related outcomes were found (Table III). Based upon GRADE D evidence, the working group considers LTRA use moderately safe during pregnancy for asthma patients. The working group advises to only use LTRAs as add-on therapy when other treatment options fail and well-controlled asthma cannot be achieved without LTRAs. Continuation during pregnancy seems reasonable if a patient is experiencing clear benefit from LTRA use prior to pregnancy.

Biologics (omalizumab [anti−immunoglobulin E], mepolizumab, reslizumab, benralizumab [anti-interleukin {IL} 5/5Ra], dupilumab [anti-IL-4/IL-13])

Recommendations (GRADE D).

- Continue omalizumab in pregnant women with asthma when their asthma is well controlled.
- Be cautious about continuing biologics other than omalizumab in women with asthma who are pregnant or planning to become pregnant owing to a lack of data. Consider these biologics only when absolutely necessary.
- Inform women, who use biologics during pregnancy, about the possibility to register on mothertobaby.org/pregnancy-study or other pregnancy exposure registries. This allows them to contribute to a greater body of knowledge about the use of biologics during pregnancy.

Rationale. No excess rates of adverse outcomes were observed in a cohort study of 169 women using omalizumab for asthma during pregnancy in 2015. The study showed 4.4% major congenital malformations, 10.9% small for gestational age, 3.2% low birth weight, 14.5% preterm birth, 0.6% stillbirth, and 8.6% spontaneous abortion. Despite the lack of a control group, these rates can be considered comparable with other populations.[44] For further comparison, the same study group conducted another prospective study with a control group. The study published in 2020 compared women who used omalizumab during pregnancy or up to 8 weeks before conception with pregnant women with moderate to severe asthma who did not use omalizumab.[42] Also in this study, no excess rates of adverse outcomes were observed (Table III).

Based upon GRADE D evidence, the working group considers omalizumab probably safe during pregnancy for asthma patients. The working group advises to only use omalizumab as add-on therapy when other treatment options fail and well-controlled asthma cannot be achieved without omalizumab.

For other biologic therapies, no studies were yet available. When using other biologics, the working group advises individual case discussion in a multidisciplinary team. Pregnant women with asthma using biologics may be advised to register in drug safety monitoring registers; for example, mothertobaby.org/pregnancy-study.

Stepping-down inhalation medication

Recommendation (no GRADE).

- Be cautious about stepping down maintenance inhalation medication during pregnancy, because maintaining well-controlled asthma and preventing exacerbations are the primary goals of treatment.

Rationale. Consider step-down of higher doses of ICS (fluticasone equivalent $>$ 1,000 μg/d) only with close monitoring of asthma control. The potentially harmful effects of higher doses of ICS during pregnancy must be weighed against the proven harmful effects of losing asthma control.[45] Consider using inflammatory biomarkers, such as fractional exhaled nitric oxide (FeNO), when titrating ICS during pregnancy.[13,46,47]

Combined maintenance and reliever therapy (low-dose ICS/formoterol "as needed")

Recommendation (no GRADE).

- In uncontrolled asthma during pregnancy, (re)consider inhalation treatment options and discuss the potential benefits and harms of low-dose ICS/formoterol "as needed" therapy versus SABA "as needed" with the patient.

Rationale. No studies were found investigating the benefits or harms of combined maintenance and reliever therapy in a specific population of pregnant patients with asthma. However, in asthma patients in general, this treatment strategy is recommended by GINA.[18] This strategy has several advantages and involves a combination of low-dose ICS with formoterol.[48,49] Because the single components of this treatment showed a beneficial risk-benefit ratio in pregnant women, the working group assumes that, for these patients, the combination of treatments also has a beneficial risk-benefit ratio.

The working group advises individually assessing the need for treatment change for these patients and discussing this with the patient. Potential advantages for combined maintenance and reliever therapy may include improved simplicity of the treatment, improved asthma control, and decreased risk of SABA overuse,[49] whereas potential disadvantages may include getting used to a new treatment regimen and a possible risk of higher cumulative dose of ICS and/or formoterol.

Predictors of negative outcomes

Recommendations (GRADE D).

- For each pregnant patient with asthma (or women with asthma planning a pregnancy), potential risk factors for complications (uncontrolled asthma, exacerbations, and/or adverse pregnancy outcomes) should be identified, treated, and/or optimized prior to pregnancy or as early as possible in pregnancy.
- The following risk factors should all be considered when assessing the risk of complications in pregnant women with asthma.

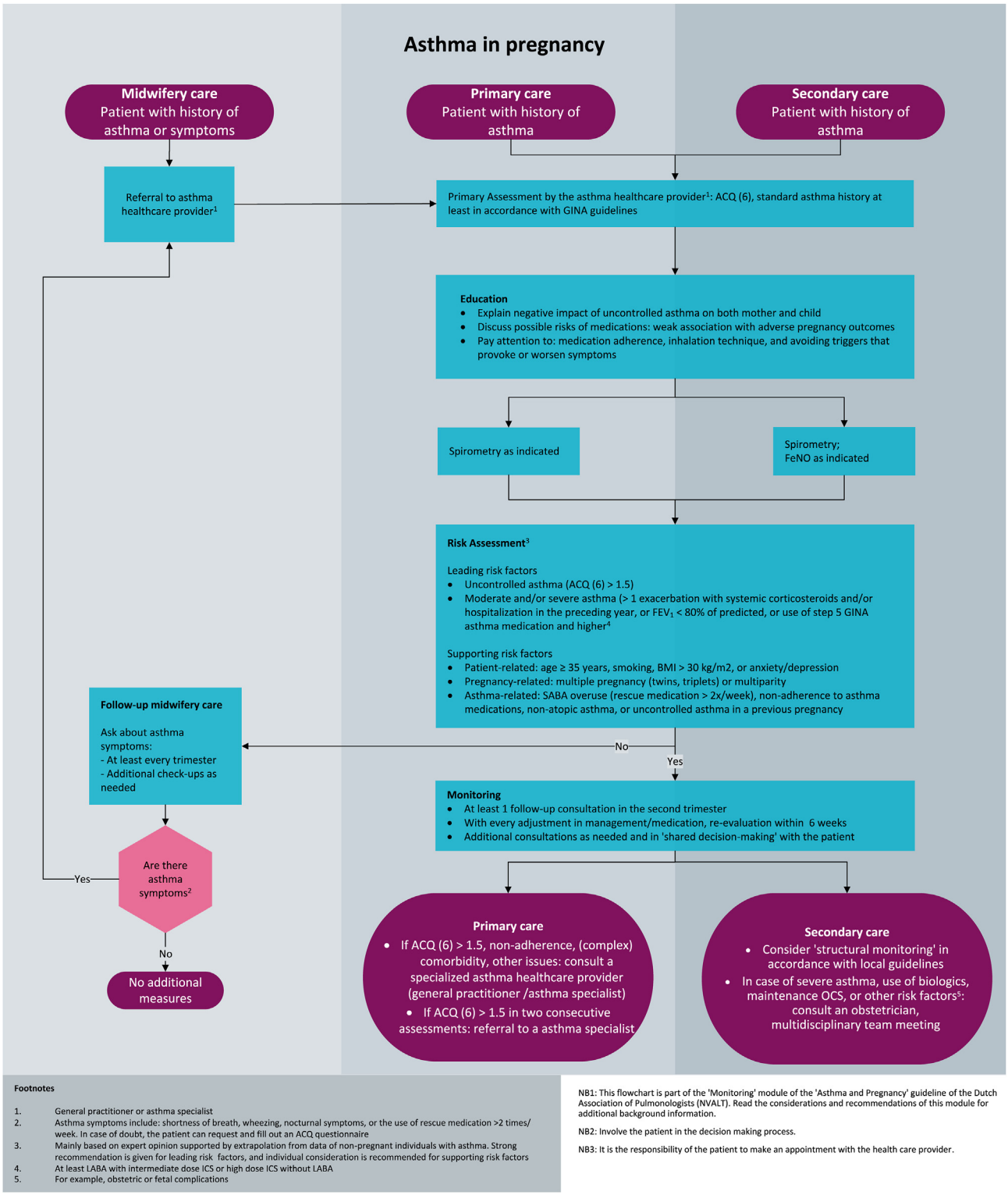
Asthma in pregnancy
Midwifery care
Patient with history of asthma or symptoms
Primary care
Patient with history of asthma
Secondary care
Patient with history of asthma
Referral to asthma healthcare provider[1]
Primary Assessment by the asthma healthcare provider[1]: ACQ (6), standard asthma history at least in accordance with GINA guidelines
Education
Explain negative impact of uncontrolled asthma on both mother and child
Discuss possible risks of medications: weak association with adverse pregnancy outcomes
Pay attention to: medication adherence, inhalation technique, and avoiding triggers that provoke or worsen symptoms
Spirometry as indicated
Spirometry; FeNO as indicated
Risk Assessment[3]
Leading risk factors
Uncontrolled asthma (ACQ (6) > 1.5)
Moderate and/or severe asthma (> 1 exacerbation with systemic corticosteroids and/or hospitalization in the preceding year, or FEV1 < 80% of predicted, or use of step 5 GINA asthma medication and higher[4]
Supporting risk factors
Patient-related: age ≥ 35 years, smoking, BMI > 30 kg/m2, or anxiety/depression
Pregnancy-related: multiple pregnancy (twins, triplets) or multiparity
Asthma-related: SABA overuse (rescue medication > 2x/week), non-adherence to asthma medications, non-atopic asthma, or uncontrolled asthma in a previous pregnancy
No
Yes
Follow-up midwifery care
Ask about asthma symptoms:
- At least every trimester
- Additional check-ups as needed
Monitoring
At least 1 follow-up consultation in the second trimester
With every adjustment in management/medication, re-evaluation within 6 weeks
Additional consultations as needed and in 'shared decision-making' with the patient
Are there asthma symptoms[2]
Yes
No
No additional measures
Primary care
If ACQ (6) > 1.5, non-adherence, (complex) comorbidity, other issues: consult a specialized asthma healthcare provider (general practitioner /asthma specialist)
If ACQ (6) > 1.5 in two consecutive assessments: referral to a asthma specialist
Secondary care
Consider 'structural monitoring' in accordance with local guidelines
In case of severe asthma, use of biologics, maintenance OCS, or other risk factors[5]: consult an obstetrician, multidisciplinary team meeting
Footnotes
1. General practitioner or asthma specialist
2. Asthma symptoms include: shortness of breath, wheezing, nocturnal symptoms, or the use of rescue medication >2 times/ week. In case of doubt, the patient can request and fill out an ACQ questionnaire
3. Mainly based on expert opinion supported by extrapolation from data of non-pregnant individuals with asthma. Strong recommendation is given for leading risk factors, and individual consideration is recommended for supporting risk factors
4. At least LABA with intermediate dose ICS or high dose ICS without LABA
5. For example, obstetric or fetal complications
NB1: This flowchart is part of the 'Monitoring' module of the 'Asthma and Pregnancy' guideline of the Dutch Association of Pulmonologists (NVALT). Read the considerations and recommendations of this module for additional background information.
NB2: Involve the patient in the decision making process.
NB3: It is the responsibility of the patient to make an appointment with the health care provider.

FIGURE 1. Flowchart for monitoring asthma in pregnant women. *BMI,* Body mass index.

1. Major risk factors
   a. Uncontrolled asthma (Asthma Control Questionnaire-6 score, ACQ-6 $\geq$ 1.5) (In accordance with the terminology in GINA.[45]
   b. Moderate and/or severe asthma: >1 exacerbation treated with OCS and/or hospitalization during prior year, or forced expiratory volume in 1 second < 80% of predicted, or use of step 5 GINA asthma medication and

higher (step 5 GINA asthma medication: at least LABA with intermediate-dose ICS or high-dose ICS without LABA), or treatment by an asthma specialist.

2. Minor risk factors
   c. Patient-related factors
      - Age $\geq$ 35 years
      - Persistent smoking
      - Obesity (body mass index $>$ 30 kg/m^2)
      - Anxiety/depressive disorder
   d. Pregnancy-related factors
      - Multiparity
      - Multiple pregnancy
   e. Asthma-related factors
      - SABA overuse (definition of SABA overuse according to GINA: more than twice a week or $>$ 2 canisters/y)
      - Nonadherence to asthma medication
      - Nonatopic asthma
      - Poor asthma control during previous pregnancy

Rationale. The current GINA guideline recommends close monitoring for all pregnant asthma patients.[45] However, this is often neither feasible nor necessary. To guide the selection of pregnant patients with asthma requiring intensive monitoring, risk factors have been identified in this guideline that predict maternal asthma-related and pregnancy-related complications and neonatal outcomes.

In a systematic literature search from 2000 until 2020, 63 studies were considered relevant. However, most studies were excluded owing to the lack of confounding adjustment. One study by Thuot et al[50] was included for direct evidence, 6 studies for indirect evidence, and an additional meta-analysis of 35 studies by Robijn et al[51] was added later and used in the considerations.

The study by Thuot et al[50] investigated the relation between body mass index and risk for "small for gestational age" and "preterm birth," but no differences were found after correction for confounding factors. In addition, in a meta-analysis, the risks for asthma exacerbations during pregnancy were associated with moderate asthma (RR 3.44; 95% CI 2.03−5.83, vs mild asthma) and severe asthma (RR 2.70; 95% CI 1.85−3.95, vs mild-moderate asthma), maternal age 35 years or older (RR 1.27; 95% CI 1.06−1.52), smoking (RR 1.35; 95% CI 1.04−1.75), obesity (RR 1.25; 95% CI 1.15−1.37), depression/anxiety disorder (RR 1.42; 95% CI 1.27−1.59); definitions were based upon questionnaire scores; multiparity (RR 1.31; 95% CI 1.01−1.68), and multiple pregnancy (RR 2.23; 95% CI 1.10-4.50).[51] Other risk factors for exacerbations that were identified were nonadherence to asthma medication (which is particularly relevant during pregnancy owing to fear for teratogenic effects),[52] low socioeconomic status,[53] late-onset and/or nonatopic asthma[54,55] (but studies were small and outcomes poorly defined). One study suggested that there was a significant concordance between the course of asthma during successive pregnancies.[56] Despite a lack of studies in pregnant patients with asthma, the working group also included SABA overuse as a risk factor because in nonpregnant patients with asthma, this factor is strongly associated with exacerbations and mortality.[57]

The working group concluded that, despite the lack of studies directly answering the Patients/Population, Intervention, Control, Outcome question, there are sufficient data to support a recommendation for clinical practice regarding patient selection for intensive monitoring based upon risk factor analysis. Most of the risk factors for complications during pregnancy are also risk factors for exacerbations in nonpregnant patients with asthma. In addition, the meta-analysis by Robijn et al[51] highlighted moderate to severe asthma as an important risk factor for exacerbations during pregnancy. Therefore, the working group decided to split risk factor analysis into major and minor risk factors. Despite this terminology, the risk factors are cumulative. All risk factors must be considered and no sharp threshold can be defined. As such, the risk factor analysis should be used as a helpful tool, but the final decision to select patients for intensive monitoring is made on an individual basis by the treating physician.

Monitoring of asthma in pregnant women

Recommendations.

- Primary assessment (no GRADE)
  - A suitably trained health care provider must perform a primary assessment for every patient with asthma in the early stage of pregnancy to (1) identify risk factors for adverse outcomes and (2) provide education.
  - Education: discuss (1) the risk of uncontrolled asthma on adverse outcomes, (2) the importance of timely self-reporting of asthma symptoms, (3) the benefits and risks of asthma medications, and (4) the risks of nonadherence, ongoing asthma triggers, (passive) smoking, reflux, and obesity.
- Monitoring frequency (no GRADE)
  - Make individual decisions about monitoring frequency using shared decision making. Include test results, the physician's risk assessment of complications, and personal preferences.
  - Patients with increased risk of complications must be reevaluated at least once in the second trimester of pregnancy.
  - Pregnant patients with uncontrolled asthma must be monitored at least every 6 weeks until treatment goals are achieved.
- Systematic structural monitoring (GRADE D)
  - Consider implementing systematic structural monitoring through regular consultation with health care providers (with minimum attention to education, asthma symptom scores (ACQ-6), and follow-up) and/or lung function (ie, spirometry) and/or self-management through an E-health application.

Rationale. Asthma is a variable disease with symptoms that change over time. Therefore, shared decision making to determine the frequency of monitoring by the treating health care provider with the patient is recommended by the working group. Test results (ACQ-6, lung function, FeNO), risk assessment, and personal preferences can be taken into account.

Evidence suggests that systematic structural monitoring may be helpful. The literature search identified 3 relevant studies. Lim et al[58] (single-blind randomized controlled trial [RCT], n = 58) showed that an intervention based upon regular patient self-monitoring improved ACQ-6 scores (−0.60 points; 95% CI −0.85 to −0.36), but did not improve asthma exacerbations or neonatal complications. Furthermore, a double-blind RCT (n = 220) showed that, by applying a FeNO-based structural monitoring system, a reduction in neonatal hospitalizations (8% vs

17%; $P = .046$) and asthma exacerbations (0.288 vs 0.496 exacerbations; number needed to treat = 6) was reached, but no improvements in other neonatal outcomes (including preterm delivery or low birth weight) or symptom-free days.[46] Zairina et al[59] (double-blind RCT, n = 72) applied a telehealth-based structural monitoring system using a handheld device and found a higher proportion of participants with well-controlled asthma (ACQ-6 < 1.5) than the control group (82% vs 58%; $P = .03$), but no significant improvement of ACQ-6 scores, neonatal outcomes, or asthma exacerbations. The working group concluded that systematic structural monitoring could be considered when all resources are available, but preferably in a research setting, and the cost effectiveness remains to be determined. Because most asthma-related symptoms in pregnant women occur between 24 and 36 weeks of gestation, and most exacerbations appear to occur in the second trimester (14−27 wk),[4,56] this may be a time when most benefit could be gained from more intensive monitoring. Therefore, in this guideline, it is recommended that pregnant women should be evaluated at least once in the second trimester.

Monitoring by the pulmonologist needs to be supported by all other caregivers. All caregivers should screen for symptoms of uncontrolled asthma (including shortness of breath, wheezing, nocturnal symptoms, or use of rescue medication > 2/wk). In addition, obstetric caregivers have a shared responsibility to refer pregnant patients with asthma with symptoms to their asthma physician at least once for a primary assessment. Furthermore, pharmacists may highlight a pregnancy in the electronic patient record and assist with medication monitoring.

The recommendations for monitoring pregnant patients with asthma are summarized in the flowchart presented in Figure 1.

Asthma medications during breastfeeding

Recommendations (no GRADE).

- Continue current asthma medication in women with asthma who are breastfeeding when their asthma is well controlled.
- Inform women about the low risk of drug therapy during breastfeeding because of minimal transmission of inhaled medications as well as biologics into breast milk.
- Based on currently available data, ICS, SABA, LABA, SAMA, LAMA, OCS, LTRA, and omalizumab can be safely continued during breastfeeding.
- For specific questions and up-to-date information concerning the safety of asthma medication during breastfeeding, consult Lactmed.[60]

Rationale. It is well known that breastfeeding has benefits for both the baby and the mother. The fact that it is not clear whether all current asthma medications can be used safely during breastfeeding does not mean that breastfeeding should be discouraged. If a woman with asthma is well adjusted to her asthma medication and wishes to breastfeed, most asthma medications can be safely continued.[19,24,45] Any effect of (inhaled) medication on the baby is expected to be small. Also, the use of OCS during breastfeeding is considered safe. Only small amounts of prednisolone (5%−25%) pass into breast milk.[60] When OCS is indicated, predniso(lo)ne is preferred.[24] Biologics are a relatively new category of medicines. Monoclonal antibodies are large protein molecules and are unlikely to pass into breast milk. In addition, these large molecules are likely to be inactivated in the infant's gastrointestinal tract. Based on limited data available on omalizumab,[21,60,61] the use of omalizumab during breastfeeding is considered safe. No safety information is yet available on the clinical use of mepolizumab, reslizumab, benralizumab, or dupilumab during breastfeeding.

CONCLUSIONS

This review of the Dutch multidisciplinary guideline on asthma and pregnancy summarizes the importance of preconception counselling, the safety of asthma medications during pregnancy and breastfeeding, and risk assessment and monitoring of asthma during pregnancy. The guideline also highlights the importance of a multidisciplinary collaboration in the management of asthma in pregnant women. Despite a lack of literature in some areas, this guideline provides structured and, where possible, evidence-based recommendations to optimize the management of asthma during pregnancy. Furthermore, a subset of unmet needs for future research has been identified by this guideline. These are as follows:

- Evaluation of the safety of biologic treatment during pregnancy and breastfeeding.
- Evaluation of the risks and benefits of low-dose ICS/formoterol maintenance and rescue therapy for asthma and pregnancy outcomes in pregnant women with asthma.
- Evaluation of structural monitoring (frequency/methods/health care providers)) of asthma during pregnancy.
- Identification of subgroups of pregnant patients with asthma who would benefit from intensified monitoring.

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REFERENCES

1. Grosso A, Locatelli F, Gini E, Albicini F, Tirelli C, Cerveri I, et al. The course of asthma during pregnancy in a recent, multicase-control study on respiratory health. Allergy Asthma Clin Immunol 2018;14:1-5.
2. Stevens DR, Perkins N, Chen Z, Kumar R, Grobman W, Subramaniam A, et al. Determining the clinical course of asthma in pregnancy. J Allergy Clin Immunol Pract 2022;10:793-802.e10.
3. Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, et al. Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol 2003;112:283-8.
4. Murphy VE, Gibson P, Talbot PI, Clifton VL. Severe asthma exacerbations during pregnancy. Obstet Gynecol 2005;106:1046-54.
5. Abdullah K, Zhu J, Gershon A, Dell S, To T. Effect of asthma exacerbation during pregnancy in women with asthma: a population-based cohort study. Eur Respir J 2020;55:1901334.
6. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. BJOG 2011;118:1314-23.
7. Rejno G, Lundholm C, Larsson K, Larsson H, Lichtenstein P, D'Onofrio BM, et al. Adverse pregnancy outcomes in asthmatic women: a population-based family design study. J Allergy Clin Immunol Pract 2018;6:916-922.e6.
8. Bakhireva LN, Schatz M, Jones KL, Chambers CD, Organization of Teratology Information Specialists Collaborative Research Group. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. Ann Allergy Asthma Immunol 2008;101:137-43.
9. Robijn AL, Brew BK, Jensen ME, Rejno G, Lundholm C, Murphy VE, et al. Effect of maternal asthma exacerbations on perinatal outcomes: a population-based study. ERJ Open Res 2020;6:00295-2020.

10. Yland JJ, Bateman BT, Huybrechts KF, Brill G, Schatz MX, Wurst KE, et al. Perinatal outcomes associated with maternal asthma and its severity and control during pregnancy. J Allergy Clin Immunol Pract 2020;8:1928-1937.e3.
11. Liu X, Agerbo E, Schlunssen V, Wright RJ, Li J, Munk-Olsen T. Maternal asthma severity and control during pregnancy and risk of offspring asthma. J Allergy Clin Immunol 2018;141:886-892.e3.
12. Mirzakhani H, Carey VJ, McElrath TF, Hollis BW, O'Connor GT, Zeiger RS, et al. Maternal asthma, preeclampsia, and risk for childhood asthma at age six. Am J Respir Crit Care Med 2019;200:638-42.
13. Morten M, Collison A, Murphy VE, Barker D, Oldmeadow C, Attia J, et al. Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma. J Allergy Clin Immunol 2018;142:1765-1772.e4.
14. Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med 1995;151:1170-4.
15. Robijn AL, Jensen ME, Gibson PG, Powell H, Giles WB, Clifton VL, et al. Trends in asthma self-management skills and inhaled corticosteroid use during pregnancy and postpartum from 2004 to 2017. J Asthma 2019;56:594-602.
16. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting, and evaluation in health care. J Clin Epidemiol 2010;63:1308-11.
17. Netherlands Respiratory Society. Multidisciplinary guideline asthma and pregnancy [in Dutch]. 2023. Accessed January 20, 2024. https://richtlijnendatabase.nl/richtlijn/astma_en_zwangerschap/startpagina_multidisciplinaire_richtlijn_astma_en_zwangerschap.html
18. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2023. Accessed June 20, 2023, https://ginasthma.org/
19. Asthma | British Thoracic Society | Better lung health for all (brit-thoracic.org.uk). Accessed July 6, 2019. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma
20. Gade EJ, Tidemandsen C, Hansen AV, Ulrik CS, Backer V. Challenges in the successful management of asthma during conception, pregnancy and delivery. Breathe (Sheff) 2022;18:220013.
21. Pfaller B, Bendien S, Ditisheim A, Eiwegger T. Management of allergic diseases in pregnancy. Allergy 2022;77:798-811.
22. Vejen Hansen A, Ali Z, Malchau SS, Blafoss J, Pinborg A, Ulrik CS. Fertility treatment among women with asthma: a case-control study of 3689 women with live births. Eur Respir J 2019;53:1800597.
23. Grzeskowiak LE, Smithers LG, Grieger JA, Bianco-Miotto T, Leemaqz SY, Clifton VL, et al. Asthma treatment impacts time to pregnancy: evidence from the international SCOPE study. Eur Respir J 2018;51:1702035.
24. Middleton PG, Gade EJ, Aguilera C, MacKillop L, Button BM, Coleman C, et al. ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. Eur Respir J 2020;55:1901208.
25. Chambers CD, Krishnan JA, Alba L, Albano JD, Bryant AS, Carver M, et al. The safety of asthma medications during pregnancy and lactation: clinical management and research priorities. J Allergy Clin Immunol 2021;147:2009-20.
26. Al Ghobain MO, AlNemer M, Khan M. Assessment of knowledge and education relating to asthma during pregnancy among women of childbearing age. Asthma Res Pract 2018;4:2.
27. Garne E, Hansen AV, Morris J, Zaupper L, Addor MC, Barisic I, et al. Use of asthma medication during pregnancy and risk of specific congenital anomalies: a European case-malformed control study. J Allergy Clin Immunol 2015;136:1496-1502.e7.
28. Eltonsy S, Forget A, Blais L. Beta2-agonists use during pregnancy and the risk of congenital malformations. Birth Defects Res A Clin Mol Teratol 2011;91:937-47.
29. Kallen B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. Eur J Clin Pharmacol 2007;63:383-8.
30. Lin S, Herdt-Losavio M, Gensburg L, Marshall E, Druschel C. Maternal asthma, asthma medication use, and the risk of congenital heart defects. Birth Defects Res A Clin Mol Teratol 2009;85:161-8.
31. Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. Thorax 2008;63:981-7.
32. Garne E, Vinkel Hansen A, Morris J, Jordan S, Klungsoyr K, Engeland A, et al. Risk of congenital anomalies after exposure to asthma medication in the first trimester of pregnancy—a cohort linkage study. BJOG 2016;123:1609-18.
33. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Hum Exp Toxicol 2006;25:447-52.
34. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. BJOG 2013;120:812-22.
35. Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. Thorax 2007;62:320-8.
36. Vasilakis-Scaramozza C, Aschengrau A, Cabral HJ, Jick SS. Asthma drugs and the risk of congenital anomalies. Pharmacotherapy 2013;33:363-8.
37. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol 2003;102:739-52.
38. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD, Organization Of Teratology Information Services Research Group. Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol 2005;116:503-9.
39. Baron AJ, Flokstra-de Blok BMJ, Kerstjens HAM, Koopmans-Klein G, Price DB, Sellink AA, et al. High use of SABAs is associated with higher exacerbation rate in Dutch patients with asthma. J Asthma Allergy 2021;14:851-61.
40. Dusser D, Ducharme FM. Safety of tiotropium in patients with asthma. Ther Adv Respir Dis 2019;13:1753466618824010.
41. Cavero-Carbonell C, Vinkel-Hansen A, Rabanque-Hernandez MJ, Martos C, Garne E. Fetal exposure to montelukast and congenital anomalies: a population based study in Denmark. Birth Defects Res 2017;109:452-9.
42. Namazy JA, Blais L, Andrews EB, Scheuerle AE, Cabana MD, Thorp JM, et al. Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. J Allergy Clin Immunol 2020;145:528-536.e1.
43. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. Eur Respir J 2013;41:1082-90.
44. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol 2015;135:407-12.
45. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Fontana, WI: Global Initiative for Asthma; 2022.
46. Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. Lancet 2011;378:983-90.
47. Murphy VE, Porsbjerg CM, Robijn AL, Gibson PG. Biomarker-guided management reduces exacerbations in non-eosinophilic asthma in pregnancy: a secondary analysis of a randomized controlled trial. Respirology 2020;25:719-25.
48. Murphy VE, Gibson PG, Schatz M. Managing asthma during pregnancy and the postpartum period. J Allergy Clin Immunol Pract 2023;11:3585-94.
49. Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. Eur Respir J 2020;56:2000625.
50. Thuot M, Coursol MA, Nguyen S, Lacasse-Guay V, Beauchesne MF, Fillion A, et al. Impact of obesity on perinatal outcomes among asthmatic women. Can Respir J 2013;20:345-50.
51. Robijn AL, Bokern MP, Jensen ME, Barker D, Baines KJ, Murphy VE. Risk factors for asthma exacerbations during pregnancy: a systematic review and meta-analysis. Eur Respir Rev 2022;31:220039.
52. Robijn AL, Barker D, Gibson PG, Giles WB, Clifton VL, Mattes J, et al. Factors associated with nonadherence to inhaled corticosteroids for asthma during pregnancy. J Allergy Clin Immunol Pract 2021;9:1242-12452.e1.
53. Carroll KN, Griffin MR, Gebretsadik T, Shintani A, Mitchel E, Hartert TV. Racial differences in asthma morbidity during pregnancy. Obstet Gynecol 2005;106:66-72.
54. Turkeltaub PC, Cheon J, Friedmann E, Lockey RF. The influence of asthma and/or hay fever on pregnancy: data from the 1995 National Survey of Family Growth. J Allergy Clin Immunol Pract 2017;5:1679-90.
55. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43:12-8.
56. Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988;81:509-17.

57. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J 2020;55:1901872.
58. Lim AS, Stewart K, Abramson MJ, Walker SP, Smith CL, George J. Multidisciplinary Approach to Management of Maternal Asthma (MAMMA): a randomized controlled trial. Chest 2014;145:1046-54.
59. Zairina E, Abramson MJ, McDonald CF, Li J, Dharmasiri T, Stewart K, et al. Telehealth to improve asthma control in pregnancy: a randomized controlled trial. Respirology 2016;21:867-74.
60. Drugs and Lactation Database (LactMed). Bethesda, MD: National Institute of Child Health and Human Development; 2006.
61. Saito J, Yakuwa N, Sandaiji N, Uno C, Yagishita S, Suzuki T, et al. Omalizumab concentrations in pregnancy and lactation: a case study. J Allergy Clin Immunol Pract 2020;8:3603-4.